Alterations in Resting Length-Tension Relations of Cardiac Muscle Induced by Changes in Contractile Force

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ABSTRACT
Effects of sustained postextrasystolic potentiation (P.S.), norepinephrine (NE), and calcium on resting length-tension relations of heart muscle were studied in the cat papillary muscle and isovolumic dog ventricle. In papillary muscles, P.S., calcium or NE produced no change in diastolic compliance when the muscles were freely isotonic, or afterloaded, and force remained constant. However, under isometric conditions, P.S. induced a small fall in diastolic tension while systolic force rose. Similar decrements in diastolic tension were observed when force of contraction was augmented by simply increasing afterload from a constant initial muscle length.

In the isovolumic ventricle, P.S., NE, and calcium each induced substantial increments in developed pressure, accompanied by small decreases in end-diastolic pressure. The latter was reduced or abolished by augmenting the initial contractile state with calcium or NE, so that the superimposition of P.S. induced only trivial increments in developed pressure.

It is concluded that P.S., calcium, or NE do not induce changes in the resting length-tension relations of heart muscle per se. However, resting length at any given resting tension does increase slightly upon the augmentation of systolic force alone. It is postulated that these findings may be explained by the existence of a series viscous component.

ADDITIONAL KEY WORDS paired electrical stimulation viscosity
distensibility series elastic element compliance calcium
series viscous component norepinephrine cat papillary muscle
dog ventricle

The effects of various interventions on the compliance of resting cardiac muscle have been of considerable interest to investigators since the turn of the century (1). While there is much evidence to the contrary (1-10), there is support for the view that the resting length-tension relation of heart muscle can be altered by various inotropic influences, such as those produced by catecholamines or sustained postextrasystolic potentiation (11-19). Since, in most experimental preparations, these interventions are associated with substantial increments in the force of contraction, we considered the possibility that the observed changes in compliance might have been mediated through increases in the systolic force per se, rather than through a direct effect of the inotropic stimulus on the muscle. The present study was undertaken to examine this proposition. If increases in the diastolic compliance of heart muscle are indeed due to alterations in the contractile system itself, as recently proposed (18, 19), they should be apparent when the muscle is contracting under either isotonic or isometric conditions. On the other hand, if changes in systolic force alone explain these findings, then no change in myocardial compliance should be observed when the stimulus acts on a muscle contracting isotonically, but should occur whenever systolic force is increased, regardless of whether or not an inotropic influence is introduced.

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LENGTH-TENSION RELATIONS OF HEART MUSCLE

Methods

The papillary muscles from the right ventricles of 10 cats, anesthetized with sodium pentobarbital (25 mg/kg), were suspended in a myograph containing Krebs solution at 30°C, equilibrated with 5% CO₂ and 95% O₂; this preparation has been described in detail elsewhere (7). Length of the muscles averaged 6.8 mm and their cross-sectional area 0.86 mm². The nontendinous end of the muscle was attached by a lucite clip at the end of a stainless steel connection to a tension transducer (Statham G 1-4-350). The tendinous end of the muscle was tied to the wire extension from an isotonic magnesium lever that had a ratio of 20 to 1 and an equivalent mass of 45 mg (20). With this arrangement, the muscle could be made to contract isotonically with a variable afterload or isometrically, and initial muscle length could be changed or kept constant. Under freely isotonic conditions, in which the preload is constant, an increase in compliance would be indicated by an increase in resting muscle length. However, under afterloaded or isometric conditions, in which muscle length is held constant, an increase in compliance would be indicated by a decrease in resting tension. The muscles were stimulated by platinum plates along their lateral aspects by an American Electronic Laboratory stimulator (model 104A). Stimuli were delivered just above threshold at a constant frequency of 18/min, and all measurements were recorded on a multichannel photographic recorder.

After the muscles had been placed in the bath they were made to contract isometrically for 1 hour. To assess the effects of various inotropic interventions on diastolic length-tension relations, the responses of the cat papillary muscles were studied under three conditions: (1) lightly preloaded isotonic contractions in which muscle length was uncontrolled and the effects on resting length were assessed at a constant preload; (2) afterloaded isotonic contractions in which resting length, preload, and systolic tension were all kept constant and the effects on resting tension were measured; and (3) isometric contractions in which muscle length remained constant while the force of contraction was allowed to increase as a result of the inotropic intervention, and the effects on resting tension were determined. In all studies, measurements were made at very high as well as at the usual sensitivities of the recording apparatus.

Experiments were also performed on the isovolumically contracting right (8 experiments) and left (3 experiments) ventricles of the dog. In the former, the right side of the heart was by-passed, as described elsewhere (21), and a distensible rubber balloon, larger than the cavity of the ventricles, was inserted and inflated so that it distended the right ventricle. The tricuspid and pulmonary valves were occluded, and a drain was placed in the right ventricle. The studies of the isovolumic left ventricle, total cardiopulmonary by-pass was established by a disposable bubble oxygenator and roller pump. A special plastic button was fixed in place below the aortic valve, and the mitral valve was closed by sutures. A balloon and drain were then placed in the left ventricle.

Results

EFFECTS OF PAIRED ELECTRICAL STIMULATION

Under isotonic conditions, sustained postextrasystolic potentiation was induced by paired electrical stimulation 34 times in 10 muscles. The load on the muscle during both contraction and relaxation was constant and generally set at 1.0 g. The extent of isotonic shortening was augmented by an average of 108 ± 5 (SEM)% during paired stimulation (Fig. 1, A). No detectable increase in resting length ever followed initiation of paired stimulation, nor did resting muscle length decrease after its cessation. Even when measure-

![Figure 1](https://example.com/figure1.png)

**Figure 1**

Effects of the induction of paired electrical stimulation (P.S.) during isotonic contractions. Records are from right to left. S.P. = single pulse. ΔL = shortening. In A, with the initiation of P.S., there is a substantial increase in ΔL, while tensions remain constant. No changes in diastolic length occur. In B, diastolic muscle length is seen at very high gain. Again, no change in diastolic length is noted during P.S.
ments were made at a very high sensitivity, an increase in diastolic length following stimulation could not be found (Fig. 1, B). Thus, with a constant preload, under isotonic conditions, stimulation induced no detectable increase in the diastolic compliance of the cat papillary muscle.

The effects of paired stimulation were also studied 22 times in 10 muscles under afterloaded isotonic conditions in which resting length and developed tension remained constant when the stimulation was applied. The extent of shortening again was augmented (Fig. 2), and paired stimulation produced no measurable decrease in the resting length in any of the experiments.

When the muscles contracted isometrically, paired stimulation always increased the force developed from an average of 3.3 g to 6.7 g in 30 experiments on 10 muscles. A small fall in end-diastolic tension occurred, averaging 59 mg (range, 20 to 180 mg) with an initial preload of 1.0 g (Fig. 3). The observed fall in resting tension occurred only when an increase in the force of contraction was induced, and in general the extent of the fall depended on the degree of increase in developed tension. The reduction in resting tension did not occur following the initial contraction but only in the ensuing beats when systolic tension was augmented (Fig. 3). Moreover, in 3 muscles when paired stimulation was applied during an augmented basal contractile state induced by elevating the calcium concentration in the bath from 2.5 to 5.5 mM, the developed force was not augmented further by paired stimulation, and resting tension did not fall (Fig. 4).

The temporal relations between the magnitude of the force developed and the induced changes in resting tension are illustrated in Figure 5, a continuous record obtained from an isometrically contracting muscle. Contraction A is the first of a sequence of 7 evoked by single stimuli following a prolonged rest period, and the “rest” contraction therefore developed greater tension than the subsequent 6 contractions. Resting tension fell from the level of 1,000 mg, when the muscle was quiescent, to 935 mg after contraction A. During the subsequent 6 contractions, it gradually rose until paired stimulation was ap-
LENGTH-TENSION RELATIONS OF HEART MUSCLE

EFFECTS OF INCREASING CALCIUM AND ADDING NOREPINEPHRINE

Experiments similar to those described with paired stimulation were performed when the inotropic state was altered by raising the calcium concentration in the bath from 0.5 to 5.5 mM in 6 studies on 3 muscles. Under isotonic conditions, increasing the calcium concentration augmented the amount of shortening, but the initial length never increased (Fig. 6, bottom). However, under isometric conditions with similar increments of calcium, the force developed by the muscle increased from an average of 2.7 g to an average of 4.9 g, and resting tension fell an average of 96 mg (range 20 to 320 mg) (Fig. 6). Similar results were obtained in 3 muscles by adding norepinephrine (10^-6 M) (Fig. 7); under isotonic conditions, resting length did not increase, but when the muscles were contracting isometrically, actively developed tension increased an average of 2.9 g and resting tension fell an average of 66 mg (range 20 to 110 mg).

EFFECTS OF INCREASING AFTERLOAD ALONE

In 19 experiments on 9 muscles, the preload was held constant and the effects on resting tension of progressively increasing afterload were determined. With each increment in afterload, a small fall in resting tension was observed, indicating that a small increase in compliance of the muscle had occurred with each increase in force development (Fig. 8).
Effects of norepinephrine (NE) on isometric and isotonic contractions. Records are from right to left. Tension in high and low gain and shortening (ΔL) are shown. Under isometric conditions addition of NE results in an increase in developed tension accompanied by a small decline in resting tension. In contrast, under isotonic conditions NE substantially increases the extent of shortening without changing resting muscle length.

Effects of progressively increasing afterload on the resting tension. Records are from right to left and are continuous. A, afterload was progressively increased. As shown by the tension tracing at high sensitivity, the diastolic tension falls progressively as the afterload is increased.

The extent of this decline in resting tension varied considerably among preparations, ranging from 3.0% to 22.6% and averaging 8.8% of the preload, in going from an isotonically to an isometrically contracting muscle. After removal of the afterload, in some muscles the resting tension returned to control levels, but in most the return was incomplete. In Figure 9, the decline in resting tension that occurred in a representative experiment is plotted against the increasing afterload. Observations were made during single stimulation as well as during paired stimulation. The two curves were essentially identical, indicating that the fall in resting tension was a function of the progressively increasing force developed by the muscle, regardless of its inotropic state.

Observations in the isovolumically contracting ventricle

In 6 experiments the effects of paired stimulation were studied in the isovolumically contracting right ventricle and in 3 on the isovolumically contracting left ventricle. In each instance the peak systolic pressure within the balloon increased (Δ 24 to 77 mm Hg), and this was accompanied by a decline in the end-diastolic pressure within the balloon, reflecting decreases in end-diastolic tension. The maximum decreases of end-diastolic pressures in the normal range (below 10 mm Hg) ranged from 0.25 to 1.5 mm Hg (Figs. 10 and 11). As shown in Figure 11, the extent of the fall was dependent on the initial level of diastolic pressure, a greater decline occurring with higher end-diastolic pressures (Fig. 11, panels B and C). When systolic force was augmented with calcium infusion (20 mM/min), end-diastolic pressure in the balloon again declined (Figs. 10, D and 11, D); however, when paired stimulation was applied

Relation between the increase in afterload and the decrease in resting tension. Note that the same fall in resting tension occurs whether the muscle is being stimulated by single (o) or double pulses (paired electrical stimulation) (•).
during the calcium infusion, there was no further increase in systolic tension nor further decline in diastolic pressure.

Discussion
The present study, based on observations made on the isolated cat papillary muscle and the isovolumically contracting dog ventricle, has demonstrated that positive inotropic interventions, such as sustained postextrasystolic potentiation, increased calcium concentrations, and addition of norepinephrine, do not by themselves induce a change in the resting length-tension relations of heart muscle. However, when the experiment is designed so that the inotropic interventions increase systolic force, small decreases in resting tension or end-diastolic pressure result, and it appears that these decreases can be attributed to the increase of systolic force alone. Indeed, similar decrements in resting tension have been observed at a constant muscle length when systolic force is increased, without altering the fundamental contractile state of the muscle, as occurs with changing from isotonic to isometric contractions, or by increasing the afterload at a constant initial muscle length.

These findings may be related to the familiar model of muscle proposed by Hill (22). In this model, muscle has three components: (1) a contractile element which is freely extensible at rest but shortens and develops force following activation; (2) an elastic component arranged in series with the contractile element, the series elastic element, which at rest is entirely passive and bears negligible tension but is stretched following activation and contraction of the contractile element; and (3) an elastic component that is parallel with the contractile element and series elastic element, the parallel elastic element, which bears essentially all of the resting tension. With activation, the contractile element

![Figure 10](http://circres.ahajournals.org/)

Isovolumic right ventricular preparation. Systemic aortic pressure (Ao.Pr.) and right ventricular pressure (R.V.Pr.) at low (middle channel) and high (lower channel) sensitivities are shown. The arrows denote the right ventricular end-diastolic pressure on the high gain trace. P.S. (B) and calcium (D) increase systolic force and reduce end-diastolic pressure. However, when P.S. is superimposed on the already augmented contractile state (E), an extrasystolic contraction still occurs, but systolic force does not increase significantly, and accordingly no change in diastolic pressure occurs.
shortens and stretches the series elastic element, thus delivering force to the external attachments of the muscle. The findings of the present study cannot be completely explained by this model but suggest that a viscous component also exists in series with the other three elements. A spring in parallel with this viscous component would provide a restoring force. It is proposed that elongation of this series viscous component, which occurs whenever force of contraction is augmented, lowers the resting tension at any given initial muscle length, and thus produces a change in compliance. The precise location and nature of this series viscous component has yet to be defined. While viscosity in the tendinous end and its myographic attachments or in a damaged portion of the papillary muscle could partially explain the findings in the isolated muscle, the demonstration of the same phenomenon in the intact heart suggests that these factors cannot account entirely for the extension of this proposed series viscous component.

When viewed in the light of the present investigation, it may be possible to explain the inconsistencies in the literature concerning the effects of various inotropic interventions on resting length-tension relations. First of all, different investigators have employed various preparations; those who have observed an increase in compliance with inotropic interventions generally have worked with isometric or isovolumic preparations (16-
18) where stray series compliances could play a role, while in many of those observations in which no increase in compliance occurred, the muscles were not contracting isometrically (2, 3, 5, 6, 10). Secondly, it is clear that the increase in compliance, resulting presumably from the stretching of a series viscous component that is induced by inotropic interventions, is relatively small, even when noted, and its detection requires high sensitivity of the recording apparatus (19). Thirdly, it is essential that ventricular relaxation be complete prior to the imposition of the inotropic influence, since the latter may abbreviate systole and accelerate relaxation. Thus, it is possible that under isometric conditions an apparent change in compliance induced by an inotropic influence might mask a true change (1, 9, 22), and under isotonic conditions, when the inotropic influence does not alter resting length-tension relations, a reduction of end-diastolic tension due to more complete relaxation may be mistaken for a true change of compliance (23). Finally, in some of the earlier studies in which changes in compliance were not observed, the increases in active tension produced by the inotropic intervention were relatively modest and probably insufficient to produce readily detectable changes in resting tension (4, 5, 7, 9).

Although reductions in resting tension were never produced by inotropic influences in muscles contracting isotonically, occasionally a change in the configuration of the resting tension tracing was observed (Fig. 2); this change was sometimes associated with a slight increase in resting tension, or a slight decrease in resting length. These alterations occurred occasionally during paired stimulation, but were most often associated with high concentrations of calcium in the bath (i.e., \( \text{Ca}^{2+} = 5.0 \text{ mM} \)). The configuration of these tracings suggests that the changes were related to so-called aftercontractions, which are known to occur under the latter conditions (24). In any case, such aftercontractions produce an apparent decrease, not an increase, in compliance of the muscle.

Several implications of the findings of these experiments are apparent. First, changes in the extension of the series viscous element would be accompanied by reciprocal alterations in the length of the contractile element, if overall muscle length were to remain constant. Thus, if muscle length were constant, a lengthening of the series viscous component induced by increasing systolic tension would yield a shorter initial contractile element length and hence a decrease in the force of the subsequent contraction. Indeed, such changes have been observed. Secondly, it has been proposed that in the intact heart an increase in impedance to ventricular ejection can induce a fundamental improvement in the contractility of the ventricle, so that following a given increment in aortic pressure, left ventricular end-diastolic pressure rises initially but declines somewhat with time. This decline in left ventricular end-diastolic pressure while the increased pressure load is sustained has been termed homeometric auto-regulation (25) and has been thought to reflect a decrease in ventricular size, and an increased contractility. From the present results it appears that part of this decline with a sustained pressure load might reflect stress-relaxation of the series viscous components of the ventricle, secondary to the increased load. A third implication of the present findings relates to mechanisms of dilatation of the ventricle following sustained systolic overload. It is conceivable that one mechanism may involve continued stress relaxation of a viscous component induced by the increased force of contraction. Were such a process to occur, it could be responsible for a larger end-diastolic volume at any given level of ventricular end-diastolic tension.

References


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